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(54) Title: A METHOD AND PRODUCT FOR CLEANING AND/OR WHITENING OF TEETH			
(57) Abstract			
<p>The invention relates to a method and a product for cleaning and/or whitening of teeth. In oral hygiene products, cysteine proteinases have been shown to have a cleaning and whitening action on the teeth. However, tissues suffer damage from an extended action of cysteine proteinases. In this invention, natural human cysteine proteinases are employed for cleaning and whitening purposes and this activity can be blocked by natural cysteine proteinase inhibitors, which are released secondarily from the products at a later stage. In particular, the use of natural cysteine proteinases and their inhibitors provides the advantage that they are man's own proteins, and therefore the risk of allergization is minimized. In addition, their enzyme kinetics is presently well known.</p>			

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A METHOD AND PRODUCT FOR CLEANING AND/OR WHITENING OF TEETH

The object of the invention is a method and a product for cleaning and/or whitening of teeth based on the use of a cysteine proteinase.

PRIOR ART**5 Cysteine proteinases and their inhibitors**

Cysteine proteinases are proteolytic enzymes which possess a cysteine residue in their active site. For the existence in an active reduced form these enzymes need an external sulphhydryl reagent. The mammalian cysteine proteinases

10 belong to the cathepsin family and among them at least cathepsins B, H, L, S, O, U, and N have been purified and classified. The first mammalian cysteine proteinase to be characterized was cathepsin B (Suominen, J. & Hopsu-Havu, V.K.: Cathepsin B in the thyroid gland. *Acta chem. Scand.* 1971:25:2531). These are distributed throughout the body but they are found especially in the kidneys, liver, and macrophages (Rinne, A., Järvinen, M., Kirschke, H., Wiederanders, B., Hopsu-Havu, V.K.: Demonstration of cathepsins H and L in rat tissues. *Biomed Biochim Acta* 1986:45;11-12:1465-1476). A part of them are active in acidic pH values but a part are active in physiological pH values, such as cathepsin S. (Kirschke, H., Wiederanders, B., Brömmme, D., Rinne, A.: Cathepsin S from bovine spleen. Purification, distribution, intracellular localization and 25 action on proteins. *Biochem J* 1989:264:467-473, and Kirschke, H., Rawlings, N.D., Barrett, A.J.: Lysosomal cysteine proteinases. Academic Press, London 1995).

In the plant kingdom, there are found cysteine proteinases such as ficin, bromelain and papain (Järvinen, M., Rinne,

30 A.: Human spleen cysteine proteinase inhibitor. Purification, fractionation into isoelectric variants and

some properties of the variants. *Biochim Biophys Acta* 1982;708:210-217).

The cysteine proteinases in the plant kingdom and those found in mammals are closely related to each other.

5 Papain is classically used in research work as a cysteine proteinase employed routinely in tests and as a proteinase for comparative research work concerning mammalian cysteine proteinases and their inhibitors. (the reference books, the inventor's own unpublished and published results (Ari Rinne
10 and Mikko Järvinen 1976-1997)).

The most numerous and best known mammalian cysteine proteinases are considered to belong to the cathepsin family. However, the mammalian cysteine proteinase inhibitors are divided into several families by their
15 structure and mode of action.

Among the mammalian cysteine proteinases are further known calcium-activated cysteine proteinases, which are considered to belong to the calpain family. Their inhibitors are called calpastatins (M. Nakamura, S.

20 Imajoh-Ohmi, K. Suzuki and S. Kawashima: An endogenous inhibitor of calcium-activated neutral proteinase in UMX 7.1 Hamster Dystrophy. *Muscle & Nerve* 14:701-708, 1991). They are also inhibited by the cathepsin inhibitor kininogen.

25 Cysteine proteinases have the property of dissolving biological material, which properties can be inhibited by using inhibitors (toothpastes Rembrant® and Yotuel®, Kirschke, H., Rawlings, N.B., Barrett, A.J.: *Lysosomal cysteine proteinases*, Academic Press, London 1995 and the inventor's own unpublished results.)

30 The following are the most important and best known so called "classical" natural (originating from the body) families of cysteine proteinase inhibitors:

1. Epidermal-SH-proteinase inhibitor or acid cysteine proteinase inhibitor (ACPI) or stefin A. This inhibitor was simultaneously discovered in the beginning of the 1970'ies by Hayashi and Järvinen (Hayashi, H. (1975): The intracellular neutral SH-dependent protease associated with inflammatory reactions. *Int. Rev. Cytol.*, 40:101-151; Järvinen, M. and Hopsu-Havu, V.K. (1975): α -N-Benzoyl-arginine-2-naphthylamide hydrolase (Cathepsin B1?) from rat skin. II. Purification of the enzyme and demonstration of two inhibitors in the skin. *Acta Chem Scand B*, 29:772-780). It is aimed to have this inhibitor named internationally as cystatin A. (Type I) (Rinne, A.: Cystatin A. Human protein data [A. Haeberli, editor, VCH Verlag, Weinheim], 3. Installment 1995; Green, G.D.J., Kembhavi. A.A., Davies, M.L., Barrett, A.J.: Cystatin-like cysteine proteinase inhibitors from human liver. *Biochem J* 1984;218:939-946; Rinne, A.: Epidermal SH-protease Inhibitor. Occurrence in human and rat tissues and in human neoplasms. Thesis. *Acta Univ Ouluensis, Ser D, Medica No. 41, Oulu 1979*).
2. Another small-molecular cysteine proteinase inhibitor, which was electroneutral at pH-values 6.0-6.5, was discovered at the end of the 1970'ies (A. Rinne, M. Järvinen, J. Martikainen, M. Alavaikko und O. Räsänen: Über das Vorkommen des epidermalen SH-Protease-Inhibitors im lymphatischen Gewebe. *Verh. Anat. Ges.* 75, S. 573-574 (1981); Järvinen, M., Rinne, A.: Human spleen cysteine proteinase inhibitor. Purification, fractionation into isoelectric variants and some properties of the variants. *Biochim Biophys Acta* 1982;708:210-217). Neutral cysteine proteinase inhibitor (NCPI) or cystatin B or stefin B. (Type I) (Rinne, A., Rinne, R., Järvinen, M.: Cystatin B. Human protein data [A. Haeberli, editor, VCH Verlag, Weinheim], 3. Installment 1995).
3. γ -trace, which is called cystatin C. (Type II) (Abrahamson, M.: Human cysteine proteinase inhibitors. Isolation, physiological importance, inhibitory mechanism,

gene structure and relation to hereditary cerebral hemorrhage. Scand J Clin Lab Invest 1988: 48:suppl 191:21-31).

4. Cystatin S. (Type II) (Isemura, S., Saitoh, E., Sanada, K.: Characterization and amino acid sequence of a new acidic cysteine proteinase inhibitor (Cystatin SA) structurally closely related to cystatin S, from human whole saliva. J Biochem 1987: 102:693-704).

5. Kininogen. (Type III). (Järvinen, M., Hopsu-Havu, V.-K.: α-N-benzoylarginine-2-naphthylamide hydrolase (cathepsin B1?) from rat skin. II. Purification of the enzyme and demonstration of two inhibitors in the skin. Acta Chem Scand 1975:B:29:772-780).

6. "Psoriasis inhibitor", for which we have recently proposed the name squamin. (Type ? (not classified so far) (Järvinen, M., Rinne, A., Hopsu-Havu, V.K.: Partial purification and some properties of a new papain inhibitor from psoriatic scales. J Invest Dermatol 1984:82:471-476).

The type I lacks sulfur bridges. The type II has two sulfur bridges. The type III has three structures of the type II and a chain responsible for kininogen activity. Cysteine proteinase inhibitors are found particularly in cellular structures which have a role in the defense mechanism, such as in granulocytes, stratified squamous epithelia, dendrites as well as in histiocytic reticular cells and in the reserve cells in prostate. (Davies, M.E. and Barrett, A.J.. Immunolocalization of human cysteins in neutrophils and lymphocytes. Histochemistry, 80:373-377, 1984). In addition to the natural cysteine proteinase inhibitors, also synthetic peptide cysteine proteinase inhibitors have been made. (Brömme, D., Rinne, R., Kirschke, H.: Tight-binding inhibition of cathepsin S by cystatins. Biomed Biochim Acta 1991:150:631-635). Cysteine proteinase inhibitors are also found in the skin of poikilothermic

animals, such as salmon and river lamprey (for example the recently found so called troms family; the inventor's own unpublished results). Cysteine proteinase inhibitors are known to inhibit the reproduction of microbes (bacteria and viruses) and/or the associated destruction of tissues (Rinne, A.: Cystatin A. Human protein data [A. Haeberli, editor, VCH Verlag, Weinheim], 3. Installment 1995; Björck, L., Grubb, A. and Kjellen, L. (1990) Cystatin C, a human proteinase inhibitor, blocks replication of Herpes simplex virus. J Virol 64, 941-943; Björck, L., Åkesson, P., Bohus, M., Trojnar, J., Abrahamson, M., Olafson, I., and Grubb, A. (1989) Bacterial growth blocked by a synthetic peptide based on the structure of a human proteinase inhibitor. Nature 337, 385-386; Björklund, H.V., Johansson, T.R., and Rinne, A. Rhabdovirus-induced apoptosis in a fish cell line is inhibited by a human endogenous acid cystein proteinase inhibitor. J Virol, 71:5658-5662, 1997).

Of course, the human cysteine proteinase inhibitors found endogenously in the mouth (in the saliva and the mucosa) make a contribution to the inhibition of cysteine proteinases. However, the ACPI, for example, is known to be reduced or lost in an inflamed or cariogenic mouth (Finnish patent FI 96743 and inventor's own unpublished results).

Controlled release of an active agent from a pharmaceutical preparation

Controlling the rate and timing of the release of an active agent, generally a medicament, from a pharmaceutical preparation is a common practice in the development of drugs. The controlled release of an active agent is applied, for example, for preparations which do not withstand the action of the gastric juice. In that case a tablet is coated with a membrane which is not degraded until in the small intestine, in which case the drug can be protected against the deleterious effects of the acidic environment in the stomach. Many kinds of pharmaceutical

preparations, in which the drug is released at a controlled rate, are also used in ophthalmology. The aim in their development has been to obtain a relatively slow release of the drug from the carrier. However, by the choice of a 5 suitable form of preparation it is possible to control the rate of release in both directions. When the so called pro-drugs are used, the drug itself is bound to a carrier in such a manner that the complex is inactive and the activation does not occur until, for example, at the mucosa 10 upon the cleavage of the bond between the carrier and the drug. Examples of such preparations are among others piv-and bacampicillin, both of which are clinically used preparations. The drug can also be activated by the pH in its environment. A well known example of this is 15 omeprazole, a drug which is used in the treatment of gastric ulcer which does not become active until upon contact with the hydrogen ion-producing parietal cells.

The pharmaceutical dosage form of a drug can be designed to release the active agent relatively quickly in the oral 20 mucosa. For example, upon the delivery of nitroglycerin as a resoriblet or a sublingual tablet, the originally solid preparation disintegrates on the oral mucosa at a conspicuously fast rate such that the effect of the drug in the bloodstream is obtained as early as in 2-3 minutes. For 25 the treatment of gastric ulcer is available on the market among others Pepcidin Rapitab tablet (MSD), which rapidly releases the drug upon contact with oral excretions; the dissolution of the tablet on the oral mucosa takes only a few tens of seconds. A two-layered tablet allows the 30 release of desired pharmacologically active agents in a chosen order. The outer layer of the tablet can be adapted to dissolve rapidly upon contact with oral excretions, whereupon the agent mixed therein is delivered quickly in the mouth; by employing excipients in the core of the 35 tablet, the core can be adapted to dissolve at a slower rate, which results in a slower release and a slower onset of the effects of the active agents mixed therein. By

using normal pharmaceutical practice it is also possible to produce preparations comprising more than two layers, which result in the ability to control the respective order of release and the onset of the effects of the active agent
5 when the product is held on the oral mucous membrane.

Liposome technique

The mixing of molecules with hydrophilic and hydrophobic properties in an aqueous solution produces vesicles, known as liposomes. The liposomes allow the encapsulation of,
10 among other things, drugs and many other biologically active agents within their interior, thereby making it possible to have a desired influence on the spectrum of actions of the respective agent in the body. The composition of the liposomal membrane, encapsulation
15 efficiency or the ability of the liposome to encapsulate the desired active agent within its interior, the stability of the preparation, the release rate of the active agent, the distribution of the liposomal preparation within the body, the size of the liposome and its surface electric
20 charge contribute, besides of other factors, to the properties of the complex composed of the liposome and the encapsulated agent, thereby making the application of the combination in various situations flexible. Insulin can be mentioned as an example of a protein structure which is
25 rather simple to encapsulate in the liposome. On the inner surface of a production vessel a thin membrane can be made of lechitin and cholesterol. The addition of a water-based buffered insulin solution and subsequent shaking results in the formation of insulin-containing liposomes. Various
30 liposome preparations are available commercially and are used widely, for example in skin care products. Catezomes TM (Collaborative Laboratories) can be mentioned as an exemplary product which can be used in the encapsulation of both hydrophilic anf hydrophobic agents and which are
35 specially designed to keep the active agent on the surface of the skin.

The problem associated with the cysteine proteinase preparations in the art

The enzymatic activity of cysteine proteinases has been exploited in the art in a cleaning and whitening toothpaste 5 (Rembrandt®, Yotuel®). In this toothpaste papain from the papaya-fruit has been used as a cysteine proteinase. Papain is a foreign protein to the mammalian body and in long term use of it is known to cause allergy at least. In addition, papain is active at an acidic pH but not at a physiological 10 pH in the oral area, as for example body's own cathepsin S. Similarly, Yotuel® chewing gum, which contains, among other things, xylitol and papain as a whitening agent, has appeared on the market quite recently.

SUMMARY OF THE INVENTION

15 The invention is directed to a method for cleaning and/or whitening of the teeth of an individual. In the method, body's own cysteine proteinase is contacted with the teeth.

The invention is also directed to an oral hygiene product, which is intended for the cleaning and/or whitening of a 20 person's teeth and which contains a cysteine proteinase and a necessary carrier. According to the invention, the cysteine proteinase is one of the man's own natural cysteine proteinases.

DESCRIPTION OF THE INVENTION

25 The terms "natural" cysteine proteinase or cysteine proteinase inhibitor and "the body's own" cysteine proteinase or cysteine proteinase inhibitor refer to substances purified by techniques in the art of protein chemistry as well as produced by molecular biological 30 techniques. Most of such cysteine proteinases belong to the cathepsin or calpain family.

In the method of the invention the cysteine proteinase is activated by contacting it with a sulfhydryl reagent, such as cysteine. For the activation, it is also of importance that the pH is suitable to the activation of the respective cysteine proteinase. The pH is suitably adjusted, if necessary, in order to activate the cysteine proteinase. Various procedures are available for the activation.

If desired, cysteine proteinase activity can be blocked by delivering a pH-controlling agent and/or body's own cysteine proteinase inhibitor into the mouth at a moment when the cysteine proteinase has acted sufficiently long. Alternatively, the action of the cysteine proteinase can be blocked by releasing into the mouth a pH-controlling agent given concurrently with the cysteine proteinase and/or body's own cysteine proteinase inhibitor.

The oral hygiene product of the invention, which is intended to cleaning and/or whitening of teeth of an individual and which comprises the body's own cysteine proteinase and a necessary carrier, can, in principle, be of any type. For example, it can be a solid, such as a chewing gum, or a tablet; a solution; a suspension; or semi-solid, such as, for example, a toothpaste.

According to the preferred embodiment, the product comprises also a sulfhydryl reagent or some other reductant necessary for the activation of the cysteine proteinase. If the ambient oral pH is unfavourable for the activation of the cysteine proteinase it is advisable that the product also contains a pH-controlling substance.

If desired, to the product can also be added an agent which blocks the cysteine proteinase and which is released after the completion of the desired duration of action of the cysteine proteinase. The agent which blocks the cysteine proteinase can be a pH-controlling agent (or an agent which blocks the active state of the cysteine proteinase) or any

of the body's own cysteine proteinase inhibitors.

The release of the agent which blocks the cysteine proteinase after a specified time has elapsed can be accomplished by employing any of the techniques known in
5 the art of controlled release.

The product can also comprise many of the body's own cysteine proteinases and possibly many of the body's own cysteine proteinase inhibitors.

The invention can be described in more detail by reference
10 to the following examples:

To a toothpaste, mouthwash, or candies is added natural human cathepsin S (this can be produced for example by molecular biological techniques), which is active at the physiological pH prevailing in the mouth. A further
15 addition is a sulfhydryl reagent, for example cysteine, which is released in the mouth from granules, see below. With the assistance of an externally added sulfhydryl reagent cathepsin S becomes biologically active and performs proteolytic cleaning and whitening in the mouth
20 and the teeth. The long-term and possibly deleterious activity of cathepsin S is inhibited with the release after a specified time into the mouth of (a) human cysteine proteinase inhibitor(s) added to the product. Also the action of cysteine proteinase inhibitors in inhibiting the
25 growth of pathogenic micro-organisms, which is known in the art, is also taken advantage of. In particular, as cysteine proteinase inhibitors known natural human cysteine proteinase inhibitors are employed.

Alternatively, the products can also be prepared so that,
30 for example, human cathepsins B, H or L are used as the natural cysteine proteinase, in which case the product has to be made such that the excipients in the product convert the oral mucosa transiently acidic, under which conditions

the respective cathepsins are biologically active. Of course, also so called "new" recently discovered human cysteine cathepsins, such as O, U, K etc., can be used once their activity ranges have been exactly determined.

5 All the proteins (cysteine proteinases and their inhibitors) associated with this invention can be produced by purifying them directly from human tissues or by using molecular biological techniques.

10 The pH in the mixture and in the mouth should return again to a physiological value secondarily in connection with the release of the inhibitor. The potency of the respective exogenously added natural cathepsins is exhausted and the natural externally added inhibitors together with the inhibitors already present orally secure additionally the
15 cessation of the proteolysis, which is deleterious in the body. The excipients in question (cysteine proteinases and their inhibitors) are added to products which are known per se (toothpastes, mouthwashes, and candy products). Many variations can be made in the basic products. Modifications
20 and fine-tuning can be made by using cysteine proteinases which differ somewhat in their biological properties. Similarly, representatives of various cysteine proteinase inhibitor families can be used.

25 Cathepsins and the sulphydryl reagent are packaged into the different phases of the products by employing for example liposomes (the pH is dependent upon the cathepsin employed), from which these are released at a controlled rate as the conditions in the environmental change upon bringing the liposomes into contact with the oral mucosa.
30 The retention time on the mucosa is dependent among other things on their electric charge (positive, neutral, negative). Thus the retention time can be controlled according to the desired goal. (Smolin, G., Okumoto, M., Feiler, S., Condon, D.: Idoxuridine-liposomal therapy for
35 herpes simplex keratitis. Am J Ophthalmol 1981:91:220-225;

Meisner, D., Pringle, J., Mezei, M.: Liposomal ophthalmic drug delivery. III. Pharmacodynamic and biodisposition studies of atropine. Int J Pharm 1989:55:105-113; Barber, R.F., Shek, P.N.: Tear-induced release of

5 liposome-entrapped agents. Int J Pharm 1990:60:219-227; Lee, V.H.L., Urrea, P.T., Smith, R.E., Schantzlin, D.J.: Ocular drug bioavailability from topically applied liposomes. Surv Ophthalmol 1985:29:335-348; Guo, L.S.S., Redema, C.T., Radhakrisnan, R.: Bioadhesive liposomes in

10 ophthalmic delivery. Invest Ophthalmol Vis Sci 1987:28:72; Finne, U.: Basic salts modify timolol delivery in ocular inserts of alkyl monoesters of poly(vinyl methyl ether-maleic anhydride). University of Kuopio, National Agency for Welfare and Health, Research Reports 15,

15 Helsinki 1991). The secondarily released cysteine proteinase inhibitor is bound for example to a mucoadhesive polymer (the physiological or slightly basic oral pH). These are synthetic or natural macromolecules [Longer, M.A., Robinson, J.R.: Fundamental aspects of bioadhesion.

20 Pharm Int 1986:7:114-117; Hui, H.W., Robinson, J.R.: Ocular delivery of progesterone using a bioadhesive polymer. Int J Pharm 1985:26:203-213; Saettone, M.F., Chetoni, P., Torracca, M.T., Burgalassi, S., Giannaccini, B.: Evaluation of muco-adhesive properties and in vivo activity

25 of ophthalmic vehicles based on hyaluronic acid. Int J Pharm 1989:51:203-212; Robinson, J.R.: Bioadhesive compositions and methods therewith. US Patent 1991:4,983,392; Finne, U.: Basic salts modify timolol delivery in ocular inserts of alkyl monoesters of

30 poly(vinyl methyl ether-maleic anhydride). University of Kuopio, National Agency for Welfare and Health, Research Reports 15, Helsinki 1991; Lahdes K: Systemic absorption and effects of topically applied ocular anticholinergic drugs, Annales Universitatis Turkuensis Ser. D, Tom. 218,

35 Turku 1996; Huupponen, R., Kaila, T., Saettone, M.F., Monti, D., Iisalo, E., Salminen, L., Oksala, O.: The effect of some macromolecular ionic complexes on the pharmacokinetics and dynamics of ocular cyclopentolate in

rabbits. J Ocul Pharmacol 1992;8:59-67]. This provides a longer lasting inhibitor on the mucous membrane, whereupon the known ability of the cysteine proteinase inhibitors to inhibit the tissue defects caused by for example pathogenic organisms (disease processes) is also specifically enhanced. Liposomes or other similar controlled release structures having mucoadhesive properties can also be used in the package.

A paced action can be obtained also by using a so called hydrogel, from which the active agent is slowly released by diffusion (Kupferman, A., Ryan, W.J., Leibowitz, H.M.: Prolongation of anti-inflammatory effect of prednisolone acetate. Influence of formulation in high-viscosity gel. Arch Ophthalmol 1981;99:2028-2029; Lewis, R.A., Schoenwald, R.D., Eller, M.G., Barfknecht, C.F., Phelps, C.D.: Ethoxzolamide analogue gel. A topical carbonic anhydrase inhibitor. Arch Ophthalmol 1984;102:1821-1824; Urtti, A.: Silmän uudet lääkemuodot. In: Biofarmasia 1986 Kuopio. Gummerus Oy, Jyväskylä 1986:44-53). If various matrices (carrier phases) are included in the same preparation, the release of active agents admixed therein is accomplished with distinct rates and different durations of existence on the oral mucosa.

If the product is made into a dry product, such as a chewing gum, the active agents can be packaged in a layered manner. The pace of the release can be controlled to obtain a more defined and clear result by packaging the active agents in different materials.

EXAMPLE

30 Toothpaste

The composition of a toothpaste can be the following:

1. Abrasive and polishing agents, for example calcium

carbonate or tricalcium phosphate, ca 50 %

2. Binder, for example aqueous silica or sodium carboxymethylcellulose, ca 3 %

3. A foam-producing non-soap-based detergent, ca 2 %

5 4. A soap-based detergent ca. 8 %

5. Humidifiers, for example sorbitol or glycerol, ca 30 %

6. Flavor and aroma, for example saccharine or xylitol (according to current trend salmiac), ca 1 %

7. 0,001 % cysteine cathepsin as such or packaged into

10 liposomes

8. 0,0001 % cysteine packaged for example in liposomes

9. 0,001 % cysteine proteinase inhibitor affixed into a mucoadhesive polymer

10. balance water.

15 The invention has significant advantages as compared to the products of prior art:

- in the same product, natural, exogenously delivered cysteine proteinases are used to obtain cleaning and whitening and, on the other hand, the excessive and

20 probably deleterious action upon tissues is blocked by using exogenously added natural cysteine proteinase inhibitors. The enzyme kinetics of these proteins is well known

- slightly differing natural cysteine proteinases and their

25 inhibitors can be used, and therefore the action spectrum becomes wide and the influence on the control can be more easily accomplished

- the temporal control of the active agents has been obtained such that it is sensitive and accurate by

30 employing liposomes, mucoadhesive polymers and hydrogel or other applications of the controlled-release technique

- the favourable (balancing, anti-inflammatory and antidestructive) effect of the natural inhibitor is not

removed immediately from the mucosa

- in the same product, it is possible to exploit in a controlled manner the beneficial effects of both the cysteine proteinase and their inhibitors

5 - both the cysteine proteinases and their inhibitors delivered externally into the body are body's own proteins, therefore the risk of sensitization is small; this is in contrast to the use of the respective proteinases and their inhibitors, which are recognized as foreign by the body and
10 derived for example from the plant kingdom.

The above mentioned embodiments of this invention are merely examples of the practice of the idea according to the invention. It should be apparent to those skilled in the art that the invention can have various embodiments,
15 which are within the scope of the following claims.

CLAIMS

1. A method for cleaning and/or whitening of the teeth of an individual, characterized in that a body's own cysteine proteinase is contacted with the teeth.
2. The method according to claim 1, characterized in that
5 the cysteine proteinase is activated by contacting it with a sulphydryl reagent or with an another reducing agent.
3. The method according to claim 2, characterized in that the pH is suitably adjusted, if necessary, on order to activate the cysteine proteinase.
- 10 4. The method according to claim 1, 2 or 3, characterized in that the activity of the cysteine proteinase is blocked by introducing into the mouth a pH-controlling agent and/or a body's own cysteine proteinase inhibitor.
- 15 5. The method according to claim 1, 2 or 3, characterized in that the activity of the cysteine proteinase is blocked by introducing simultaneously with the cysteine proteinase into the mouth a pH-controlling agent and/or a body's own cysteine proteinase inhibitor.
- 20 6. An oral hygiene product, which is intended for the cleaning and/or whitening of the teeth of an individual, and which comprises a cysteine proteinase and a necessary carrier, characterized in that the cysteine proteinase is one of the body's own cysteine proteinases.
- 25 7. The product according to claim 6, characterized in that it comprises a sulphydryl reagent necessary for the activation of a cysteine proteinase and optionally a pH-controlling agent.
8. The product according to claim 6 or 7, characterized in

that it also comprises an agent for blocking the activity of cysteine proteinase, said agent being released after the desired duration of action of the cysteine proteinase.

9. The product according to claim 8, characterized in that
5 the agent for blocking the activity of cysteine proteinase
is a pH-controlling agent.

10. The product according to claim 8, characterized in that
the agent for blocking the activity of the cysteine
proteinase is a body's own cysteine proteinase inhibitor.

10 11. The product according to any of the claims 6 - 10,
characterized in that it comprises several of the body's
own natural cysteine proteinases and probably several of
the body's own natural cysteine proteinase inhibitors.

12. The product according to any of the claims 6 - 11,
15 characterized in that it is a solid, such as a chewing gum
or a tablet; a solution; a suspension; or semisolid, such
as, for example, a toothpaste.

INTERNATIONAL SEARCH REPORT

1

International application No.

PCT/FI 98/00001

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 7/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CA, MEDLINE, BIOSIS, EMBASE, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Patent Abstracts of Japan, & JP,A,8157352, (TAKANO TOSHIO)18 June 1996 --	1-12
X	DE 2714718 A1 (LABORATOIRES MANCEAU S.A.), 6 October 1977 (06.10.77), the claims --	1-12
X	Journal of esthetic dentistry, Volume 3, No 2, 1991, T.C. Lyon Jr. et al, "Evaluation of Effects of Application of a Citroxain-Containing Dentifrice" page 51 - page 53 --	1-12

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 1998	30 -04- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Palmcrantz Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00001

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	File WPI, Derwent accession no. 75-02100W, Unilever LTD: "Zinc ion and enzyme contg dentifrice for reduction of dental plaque and calculus", CA,A,959764, 741224, DW7502 --	1-12 ~
A	FI 96743 B (RINNE, ARI ENSIO), 15 May 1996 (15.05.96) -----	4,10-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/04/98

International application No.

PCT/FI 98/00001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2714718 A1	06/10/77	BE 853053 A FR 2345998 A,B NL 7703670 A	30/09/77 28/10/77 04/10/77
FI 96743 B	15/05/96	FI 943964 A	01/03/96